



On the use of positron counting for radio-Assay in nuclear pharmaceutical production



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ABSTRACT

Current techniques for the measurement of radioactivity at various points during PET radiopharmaceutical production and R & D are based on the detection of the annihilation gamma rays from the radionuclide in the labelled compound. The detection systems to measure these gamma rays are usually variations of NaI or CsF scintillation based systems requiring costly and heavy lead shielding to reduce background noise. These detectors inherently suffer from low detection efficiency, high background noise and very poor linearity. They are also unable to provide any reasonably useful position information.

A novel positron counting technique is proposed for the radioactivity assay during radiopharmaceutical manufacturing that overcomes these limitations. Detection of positrons instead of gammas offers an unprecedented level of position resolution of the radiation source (down to sub-mm) thanks to the nature of the positron interaction with matter. Counting capability instead of charge integration in the detector brings the sensitivity down to the statistical limits at the same time as offering very high dynamic range and linearity from zero to any arbitrarily high activity.

This paper reports on a quantitative comparison between conventional detector systems and the proposed positron counting detector.

1. Introduction

PET radiopharmaceuticals are produced as diagnostic agents for numerous clinical areas in medical imaging. A detailed review of the radiopharmaceutical production process can be found in (Sampson, 1999). In brief, the production process involves incorporating a radionuclide, that can be produced by numerous different methods i.e. on a cyclotron or on a radionuclide generator, into a biological molecule. Automated synthesisers are used to remotely perform the radiolabelling of molecules in lead lined hotcells to reduce operator exposure to radiation. Once the radiolabelling is complete the PET radiopharmaceutical needs to be purified, often using high performance liquid chromatography (HPLC) and formulated into a patient injection. Calibrated ionisation chambers are then used to measure the final radioactive concentration of a final patient vial (single or multi dose vials). Before a radiopharmaceutical can be released for patient use a number of quality control tests need to be conducted to ensure the product quality is acceptable. For example, a gamma spectrometer is

used to determine the identity of the radionuclide present and the radionuclide purity. Determination of radiochemical purity is also required using radiodetection and either HPLC or thin layered chromatography (TLC). Typically, a radiopharmaceutical with a radiochemical purity of greater than 95% is considered acceptable for patient injection.

Current techniques for the measurement of radioactive content (RAC) of PET radiopharmaceuticals at various stages through the production process are based on the detection of the annihilation gamma rays from the positrons emitted from the active radionuclide in the radiopharmaceutical (reviewed by (Cherry)). The detectors required to measure these photons with high precision are bulky and provide little or no position resolution due to the elevated energy of the gamma ray 511 keV which requires the detector to be made from high Z materials and have a minimal size in order to maintain a reasonable detection efficiency. For example, high density scintillators such as NaI and CsF with photomultiplier tubes (PMTs) are currently used to measure radiochemical purity but these suffer from poor linearity at

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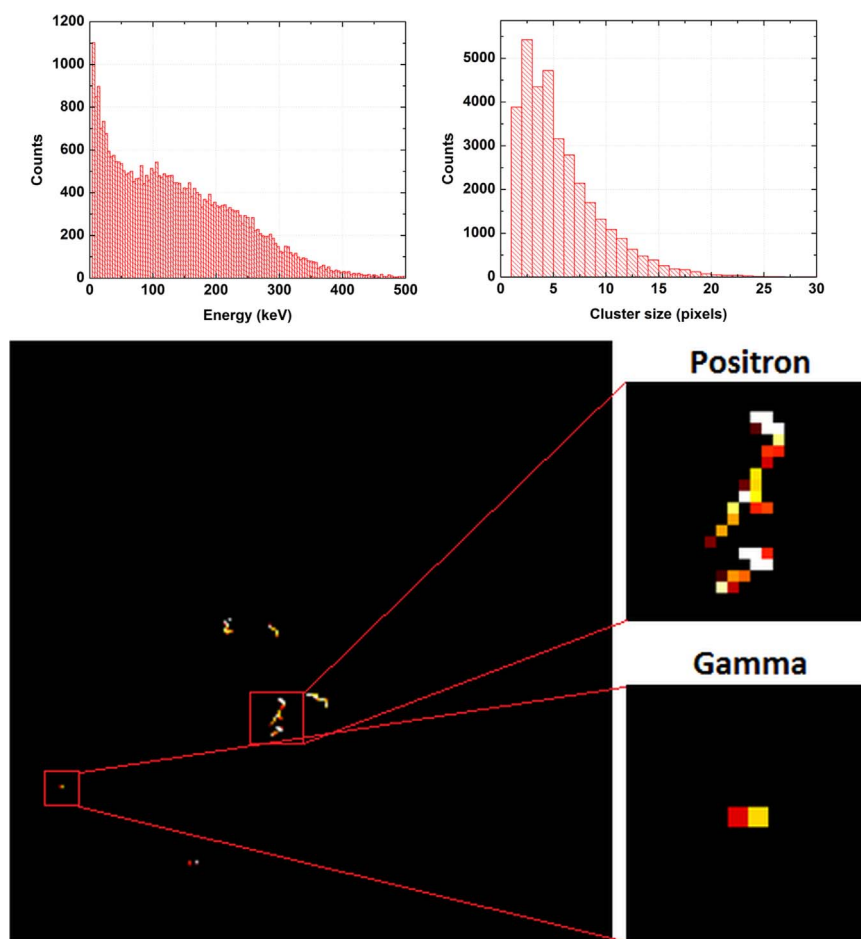


Fig. 1. Distribution of positron energy incident on the Timepix detector operated in ToT mode is shown in the top left graph. Note that the spectrum is modified by the loss of energy as the positrons pass through the Teflon tube. The graph on the top right shows the average number of pixels hit per positron for this measurement. The panel below depicts single positron and gamma interaction in the detector operating in ToT mode.

high levels of radio activity and poor energy resolution. Furthermore, the configuration of these detectors does not provide any measurement of sample radioactivity as a function of the position of the sample.

The use of a suitably configured silicon pixel detector to measure the positron output directly from a radioactive sample will dramatically improve both the linearity of the measurement and provide relatively precise information about the location of the positrons in applications such as novel micro-fluidic production platforms. The silicon detector measures the charge created by the loss of kinetic energy of the positron as it passes through the silicon. In the case of ^{18}F the positron is emitted from a proton in ^{18}F decaying to a neutron and releasing a positron and a neutrino. The positron energy has a continuous spectrum with an end point of 634 keV and a mean positron energy of 250 keV. This energy is dissipated along the path of the positron according to Bragg's Law or until the positron annihilates. For each 3.6 eV deposited in the silicon an electron hole pair is created and so the passage of the positron may be detected by measuring this charge. The spatial resolution of this measurement is only limited by the spatial resolution of the pixel detector used and does not depend on measuring the total path of the positron in the silicon (although this can also be improved by measuring the energy deposition per pixel and fitting to a Bragg curve). Monte Carlo simulations show that 87% of incident positrons each with a kinetic energy of 635 keV will pass through 300 μm of silicon leaving about 60 keV of energy in the detector material. As the energy of the incident positron decreases, the specific energy loss (outside the Bragg peak) in the detector increases. The detection of 60 keV energy loss in the silicon is easily registered in an optimized pixel detector where each pixel is sensitive to energy losses of a few keV deposited in the pixel

volume.

The use of positron counting offers several advantages in the field of radiopharmaceutical production as the actual positrons are very easily absorbed by a little material (unlike the gamma rays they produce) and so may be very effectively shielded. This enables the use of very compact (e.g. micro-fluidic) devices for the production that could have several assay points measured on a single detector - each being very well isolated from the other through judicious design of the production device layout. Such a concept has been demonstrated in (Thonon, 2013), but its usability is limited to radio-HPLC application only.

The purpose of this article is to demonstrate the potential of this type of measurements for the effective assay of RAC in radiopharmaceutical R & D and routine production. The principle difficulty is to find an appropriate method to present the positrons to the detector as any intervening material can easily absorb the positrons leaving the detector to count only the gamma induced background. Silicon is largely insensitive to photons with an energy above 20 keV and so the detector counts primarily scattered photons when the positrons are absent. As these are created all about the active sample there is no spatial distribution across the surface of the detector. This is not the case when a source of positrons that can impinge on the detector is near its sensitive volume.

2. Materials and methods

2.1. Positron counting detector

The detection system used for these measurements was a 300 μm

thick silicon detector with a 256×256 array of pixels, each of $55 \mu\text{m}$ on a side, giving a total detector active area of 1.96 cm^2 . The detector is bump bonded to a Timepix (Llopert, 2007) readout chip which processes the signals coming from each pixel individually. The readout chain for each pixel comprises a low noise charge sensitive amplifier followed by a discriminator and then a block of configurable counting logic. The pseudo-random counter is implemented on a shift register with XOR feedback which can be daisy chained to its neighbouring pixels and operated as a shift register during the readout phase and allows for very compact layout of the pixel.

The Timepix chip can be set up to operate in two modes of interest to this study:

- In counting (or Medipix) mode a threshold is set on the discriminator and any pulses above this value are counted on a 14 bit counter (max. count is 11810).
- In Time-Over-Threshold (ToT) mode the pulse triggers a local clock and the clock ticks are counted while the pulse remains over threshold. This yields a value of the pulse width (which is proportional to pulse height) for each individual pulse, hence providing energy of incident particle.

These distinct modes of operation allow to look at the total energy deposited by each positron at low activities (such that there is no double counting of positron hits by individual pixels) so one can look at the spectrum of energy deposited by the positrons in the silicon detector as shown in the top left part of Fig. 1. It was also possible to investigate the way the positrons deposited energy in the pixels and so look at the cluster size distribution. This is shown in the top right part of Fig. 1.

The detector system used in these experiments comprised of a Timepix detector, FitPix USB 2.0 readout system (Kraus,) and Pixelman data acquisition software (Holy, 2006). The whole system can fit on an adult's palm and capable of operation from a single USB cable and a PC or laptop.

The first principle issue that needed to be understood from this study was the position of the saturation point for the linear response of the system. This is a limitation with the scintillator-based techniques measuring gamma activity that are currently in use (Cherry, , Knoll,). The amplifier on each pixel has a shaping time of about $1 \mu\text{s}$ and so there should be very little double pulsing on the front end if the pixel count rate is kept well below 1 MHz per pixel. This gives a maximum supportable count rate of 40 MHz/mm^2 in order to maintain linearity. If the inner bore of the Teflon tube is taken as the portion of the array that counts at the maximum and is set to 0.8 mm inner diameter then the cross sectional area of the tube is 0.502 mm^2 and $1 \mu\text{L}$ of RAC fills a 1.25 mm length of tubing. The detector counts over 14 mm and a 0.8 mm slice across this area 14 mm^2 should be able to measure an activity of over 5 GBq/mL without any loss of linearity. A calibration of the Timepix detector system and a CsF scintillator based PMT detector against solutions of known activity was performed.

The second key aspect of the overall system performance to be investigated was minimum detectable activity signal. Positrons have different mechanism of interacting with silicon compared to gamma photons. In principle, every positron which reaches the detector through tubing and air gap with sufficient remaining energy, will interact in the detector, producing visible signal. However, significant number of positrons are lost in the relatively thick tubing. In addition, high energy gammas also interact in the detector medium producing contaminating signal. Some of these can be discriminated by analysing the shape and location of interacted particle. Positrons have curly shape spreading across many pixels, compared to gammas which tend to have localised interaction of up to 5 pixels in a cluster. A typical positron and gamma interaction in the detector medium can be seen in Fig. 1.

2.2. Experimental setup

For the measurement of *linearity*, the Timepix detector system was setup on a Teflon line that was the outflow from the CsF PMT reference detector which was fed through a PEEK line from the output of the column of a Waters Acquity UPLC® system. Eighteen different sample concentrations of ^{18}F solution, ranging from 4.95 MBq/mL to 2341.8 MBq/mL were injected onto the column ($20 \mu\text{L}$ injection volume). The analogue signal from the CsF PMT detector was integrated over the time duration of the signal and this area was used to represent the activity in MBq/mL as measured by the CsF PMT detector. The Timepix detector operated in counting mode in order to capture the passage of all the activity and the detector was readout in 150 frames, each of one second duration. The total number of counts integrated over the exposure was used as the measure of the activity of the sample. It should be noted that no shielding was in place for this measurement.

The Timepix system *sensitivity* studies were performed in the similar fashion on a different HPLC system and reference detector. The Timepix system was attached to the Teflon line outflowing from a BGO reference detector. The RAC was fed to the detectors through the Dionex Ultimate 3000 HPLC system (with no HPLC column). 11 vials with different concentration of ^{18}F solutions were prepared and measured on a dose calibrator before being injected into the HPLC lowest activity first. The concentration of ^{18}F solutions injected into the system ranged between 300 Bq/mL and 190 MBq/mL ($10 \mu\text{L}$ injection volume). The output voltage from the BGO detector was integrated under the peak representing measured activity in MBq/mL . The Medipix detector was operating in counting mode, taking one frame a second. The number of counts recorded on the detector under the tube were summed. The measured number corresponded to the measured activity in MBq/mL . For this measurement, the Timepix detector was enclosed in the background protective 1 mm thick lead shielding.

For measurement of *dynamic range*, the Timepix detector was placed on the Teflon tube of 0.8 mm internal diameter used for the transfer of the activity produced by the cyclotron to the radiochemical hot cells. The objective of this measurement was to see if this activity would saturate the detector since all the ^{18}F activity generated by the $^{18}\text{O}(\text{p},\text{n})$ nuclear reaction on a ^{18}O -water target of 2.5 mL pass via this transfer line. The total activity delivered by the cyclotron to the hot cells was of 117 GBq.

There are two considerations that could impinge on the linearity of the detector system. The absolute count rate per pixel is the first limiting factor but the linearity can also be affected by the total number of counts in each pixel as the counter depth is fixed at 14 bits and if this is exceeded it results in a loss of linearity. In order to counter this, it was decided to open the shutter for 1 ms at a time and readout frames at the highest rate possible with the USB system.

In addition to the linearity, sensitivity and dynamic range, the imaging capabilities of the Timepix detector were studied to understand its usability in Thin Layer Chromatography (TLC) applications. First a standard TLC plate was prepared according to the common practices at the Cyclotron Research Centre (CRC). $1 \mu\text{L}$ of ^{18}F radiopharmaceutical solution was deposited on the TLC plate and developed for 15 min. The plate was then examined with the Timepix detector system to understand if the measurement of activity with $55 \mu\text{m}$ pixel spatial resolution could provide any additional information.

Finally, the Timepix detector system imaging capabilities were systematically studied to assess limitations of the technology for novel developments towards micro-fluidic radiopharmaceutical production. A set of three inserts which can hold up to one, two and three standard Polyethylene tubes respectively were printed from an ABS plastic on a 3D printer. Three PE50 1.57 mm outer diameter tubes were mounted over the Timepix positron counting detector. The tubes were filled with three levels of activity, 100 kBq/mL , 10 kBq/mL and 1 kBq/mL . The aim of this study was to understand how many tubes containing ^{18}F can be assayed on one Timepix chip simultaneously without interfering

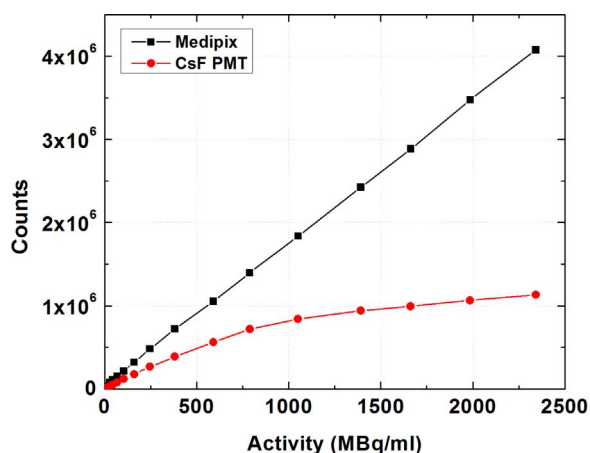


Fig. 2. Comparison of a CsF scintillator PMT and the Timepix detector for measuring different concentrations of ^{18}F -solution injected on to a HPLC system. The counting of single positrons is inherently linear in the absence of any saturation effects.

with its neighbours. In addition, it was studied how different levels of ^{18}F in the neighbouring tubes were affecting the measurement.

3. Results and discussion

3.1. Linearity

Linearity is the first fundamental advantageous property of positron counting compared to charge integration systems. The data set was acquired as described in detail in Section 2.2. Plots of these data shown in Fig. 2 show the linearity of the CsF PMT detector system begins to fall off above a RAC of around 800 MBq/mL. Below this activity the CsF detector is reasonably linear and provides the radiochemical purity measurements for the radiopharmaceutical productions performed at the CRC. The Timepix positron counting system behaves in a linear fashion for the whole measured range and beyond. The Timepix pixel electronics designed such it is capable of sustaining high count rates with theoretical limitation beyond any practical level of activity to be handled at a radiopharmaceutical manufacturing site or in R&D facilities.

This property of the system is seen advantageous not only when high and low levels of activity to be handled in one measurement run, but also when short-lived positron emitting isotopes such as ^{11}C are involved. This gives an opportunity to assess compounds without the need to wait for decay to the level acceptable to handle by the conventional detectors.

3.2. Sensitivity

Sensitivity of Timepix positron detector was compared to a conventional BGO detector system operational for the quality control of the R&D radiopharmaceuticals. The details of the experimental setup are described in Section 2.2. The comparison of two systems was made over the activity range normally handled in the radiopharmacy laboratory setting. The BGO detector can handle signals produced by activities up to 100 MBq/mL. The signal of the system becomes comparable with noise when level of activity injected is below 500 kBq/mL. It should be noted that the BGO detector remains linear over its operational activity range. As can be seen from Fig. 3 the Timepix detector produces detectable signal down to 1 kBq/mL of activity injected through the HPLC system. The detector remains sensitive in the region below 1 kBq/mL, but the laboratory radiation background contaminates useful signal, making Timepix detector unusable for practical purposes below such a level.

It is anticipated that the smallest detectable level of activity can be brought down even further. This can be achieved in two ways. The

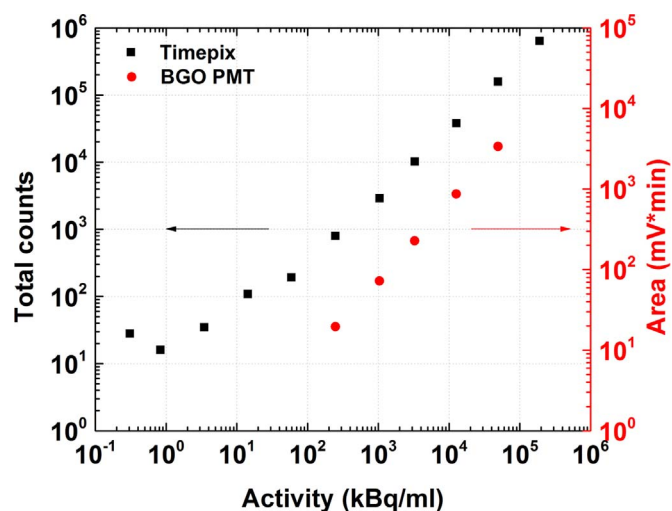


Fig. 3. Measurement of the sensitivity of the Timepix detector compared to a BGO scintillator and PMT. Measurable signal was observed down to the activity levels of 1 kBq, which was measured to be background level of the laboratory environment.

Timepix detector can be shielded even further with a combination of lead and metal to reduce background and scattering incident on the detector. Secondly, the radiation incidence rates on the detectors at these activities are small to such a level that individual interactions can be discriminated. This opens opportunity to enable Time-over-Threshold mode operation and subsequent analysis of each particle with charge-shape analysis discrimination of background gammas always present at a radiopharmacy production facility or R&D laboratory.

3.3. Dynamic range

The cyclotron used in this study irradiates an ^{18}O enriched water sample with protons of 18 MeV in order to produce the ^{18}F -Fluoride that is used to manufacture the ^{18}F -fluorinated radiopharmaceutical such as ^{18}F -FDG in the hot cells of the manufacturing facilities. After irradiation of the target for a predetermined time the 3.5 mL target volume in the cyclotron has a RAC of 117 GBq and is transferred to the hot cells via a Teflon tube shielded in a lead tunnel by flushing the tube with Helium at about 2 bar pressure. The Timepix system was placed underneath the tube and operated remotely so that the dose to the operators could be reduced to a safe level. The graph in Fig. 4 shows the normalized counts as a function of time as the dose is transferred from the cyclotron.

The main activity passes through the tube in a fraction of a second (between 1200 and 1300 ms) and the spikes that are seen after this are drops that follow the main charge. All of this can be clearly seen on the PC screen in real time where the drops are clearly imaged as shown in the inserts in Fig. 4. The maximum count in any pixel during the transfer was 16 which, for a shutter time of 1 ms, indicates that the device was operating far from any form of saturation.

3.4. Imaging capabilities

In addition to linearity, sensitivity and dynamic range measurements imaging capabilities of the device were assessed using the TLC technique. Conventionally, this is measured at present using a scintillator-based PMT attached to a scanning gantry. The detector moves over the sample, plotting the activity as a function of position. Such a system requires a collimator attached to a PMT leading to an inevitable trade-off between desirable position resolution and sensitivity of the system. If this limitation can be overcome with the positron counting technique such an improvement would have two major implications:

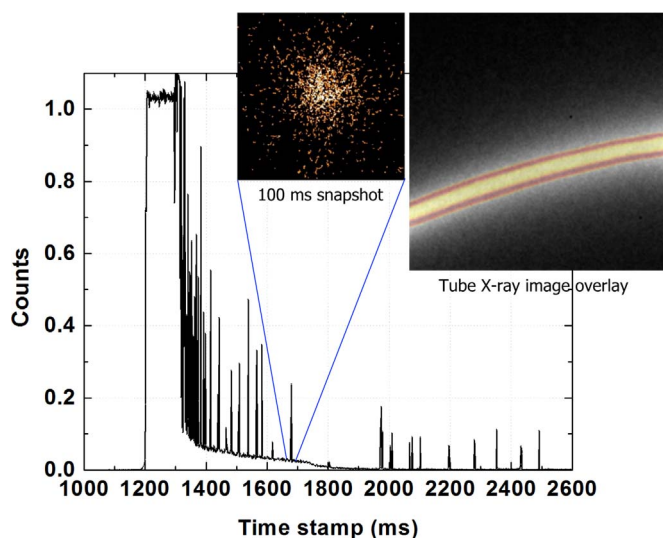


Fig. 4. Normalised counts from the passage of an activity of 117 GBq of ^{18}F measured by positron counting on the Teflon feed from the cyclotron to the hot cells at the CRC. Tube X-ray image overlay insert: distribution of positrons incident on a pixel detector when the activity sample is presented to the detector flowing through a thin walled Teflon tube. Snapshot insert: single frame of cyclotron feed after the main activity has passed showing the passage of a droplet being blown along the tube by the helium driver.

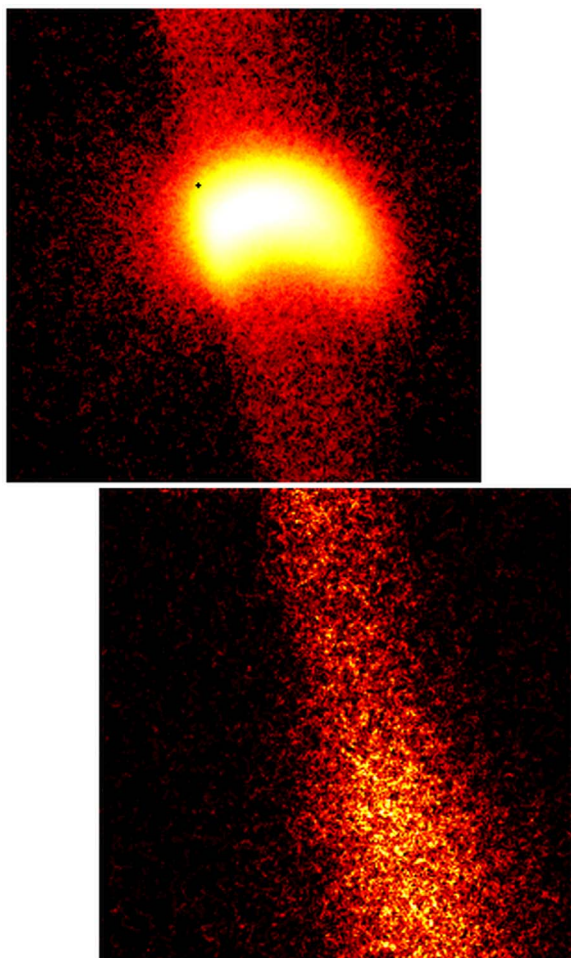


Fig. 5. ^{18}F -solution activity imaged along a TLC trace showing the variation of activity along the trace with sub-mm spatial precision.

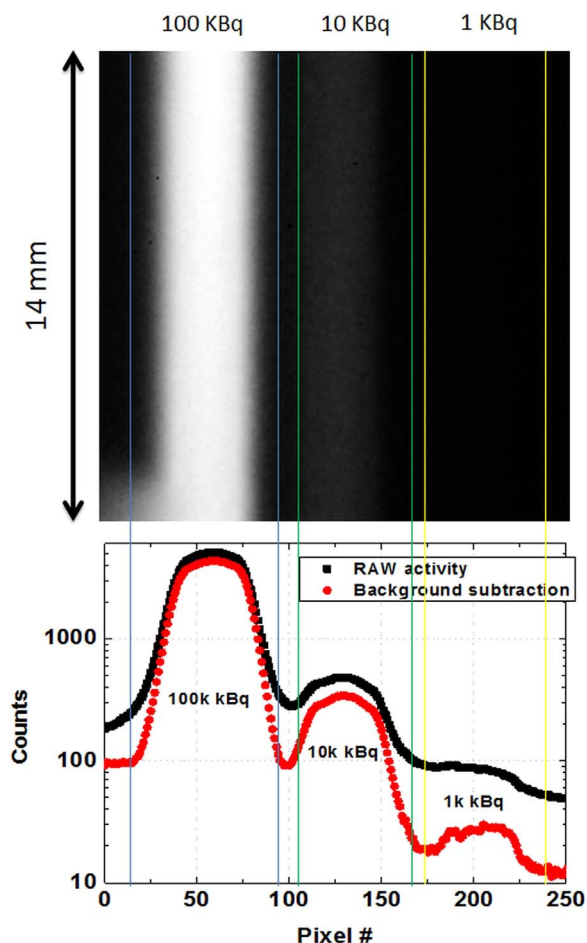


Fig. 6. Spatial resolution of the Timepix detector system was measured by placing 3 tubes over the detector area. Each tube was filled with different concentration of the ^{18}F -solution. An algorithm was developed to correct for gamma background affecting neighbouring tubes.

enabling lower activity level impurities to be identified and more importantly, the time to develop a TLC plate can be reduced maintaining the same quality of information extracted from the TLC plate. This is particularly important and any QC test has to be performed prospectively before a radiopharmaceutical can be administered to a patient.

A standard TLC plate used for the determination of radiochemical purity was prepared and developed for this experiment. As the plates used for TLC are much larger than the active area of the Timepix chip, the plate width was adjusted to 15 mm. It was scanned by manually moving the sample over the detector.

The image in Fig. 5 show the distribution of the activity on the TLC plate after migration. The upper part of the TLC plate show where the principal activity has moved as well as the lower part of the TLC with the residual activity ($R_f = 0$).

3.5. Spatial resolution

In this study the imaging performance of the positron counting system was quantified. It was necessary to understand how having multiple tubes and levels of radioactivity over the detector affected its performance. For these experiments a tube container capable of holding up to three tubes was printed on a 3D printer. A snapshot image recorded on the detector and the summed profile along the Y-axis is shown in Fig. 6. The tube containing a ^{18}F solution concentration of 100 kBq/mL clearly dominates the total amount of the recorded counts, while 1 kBq/mL can be barely seen due to an excessive background from the neighbouring tubes, see 'Raw activity' black line in Fig. 6.

A background subtraction algorithm was developed to enhance quality of the image. In order to estimate the background and describe it mathematically, a snapshot image and summed profile along the Y-axis was recorded for the central tube only, covering the detector surface to block the positron interactions. The sensor gamma response under the tube was fitted with a Gaussian function, while the detector signal outside the tube was approximated with an exponential decay function. Convolution of these two resulted in the background approximation function, which was subtracted from each tube in Fig. 6. The results of the subtraction are labelled as 'Background subtraction', shown by the red line. By applying this algorithm it was possible to recover distinct 1 kBq/mL and enhance two other peaks.

4. Conclusions

This paper describes a novel technique for use in radiopharmaceutical production and development, where measurements of positron emitting radioisotope may be accomplished with much greater accuracy through the direct detection of the positrons. Traditional detection methods of measuring the annihilation gamma emission of the positrons are inherently less linear and incapable of providing any meaningful position resolution whereas direct positron detection can measure activity with great linearity and provide very precise position information about the location of the activity. This ability to locate ^{18}F during the radiochemical synthesis is of crucial importance when developing novel radiopharmaceuticals utilizing micro-fluidic techni-

ques. A quantitative comparison between proposed Timepix positron detection system and conventional PMT based detectors show significant improvement in linearity, sensitivity and position resolution. In addition, unprecedented dynamic range of the system offers new avenues in monitoring of the cyclotron production transfer in real time.

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